REMARKS

Claims 1, 5-8, and 10-20 are pending in the above captioned patent application. Claims 1, 5-8, and 10-20 are rejected in the Office Action mailed September 17, 2002. The Examiner made the following rejections:

(1) Claims 1 and 5-8 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the Applicants regard as the invention.

(2) Claims 1, 5-8, and 10-20 were rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. patent 4,647,675 to Mayer *et al.*, in view of U.S. patent 4,900,686 to Arnost *et al.* and / or U.S. patent 5,846,737 to Kang.

The Applicants rebut the rejections in the same order presented in the Office Action referenced above.

1. The Claims Are Compliant With 35 U.S.C. § 112 (Second Paragraph)

A. The Examiner Has Misapplied The Law

At the outset, applicants must strongly protest the Examiner's continued reliance on *Ex parte Fressola* for the proposition that "A claim must stand alone to define the inventions, and incorporation into the claims by express reference to the specification or an external source is not permitted" (see Office Action pg 3). Applicants previously noted that the *Fressola* case dealt with an OMNIBUS claim:

> Claims in utility applications ... that define the invention entirely by reference to the specification and/or drawings, so-called "omnibus claims" or "formal" claims ... are properly rejected under § 112 ¶ 2 as failing to point out and distinctly claim the invention.

Ex parte Fressola, 27 USPQ 1608, 1609 (BPAI, 1993). The actual claim at issue in the *Fressola* case was Claim 42, which read as follows:

> 42. A system for the display of stereographic three-dimentional images of celestial objects *as disclosed in the specification and drawings herein.*

Thus, the *Fressola* claim DID make an "express reference" to the specification *in the claim.* Indeed, this is characteristic of the so-called OMNIBUS claim.[1]

By contrast, the Applicants' claims make no such reference to the specification. **INDEED, APPLICANTS' CLAIMS ARE NOT OMNIBUS CLAIMS!** Consequently, the holding in the *Ex parte Fressola* opinion has no bearing on the claims at issue.

The Examiner cannot use the *Fressola* holding against claims which are not omnibus claims. Moreover, the Examiner certainly cannot make the *Fressola* case into something that it is not, namely a ruling that demands that the "reaction times, pH, equipment" and the like be put in the claims.

Unfortunately, the Examiner has once again made the *Fressola* case the centerpiece of the Examiner's 112 rejection of the present claims. This is gross error on the part of the Examiner. Applicants alerted the Examiner to this error months ago (see the Response dated August 5th of 2002) - and yet the Examiner, without so much as a comment about the omnibus claim distinction, simply re-asserts *Fressola*. This is not proper examination of a patent application. An Examiner is not free to ignore the arguments made by Applicants. An Examiner is not free to misapply the case law.[2]

The Examiner is reminded that this application was filed in 1999. The Examiner is also reminded that the gross error mentioned above was perpetuated in this matter through three FINAL office actions - which necessitated additional filing fees - over a period of years! This must stop. Respectfully, applicants demand that - on the record - the Examiner admit 1) Applicants' claims are not omnibus claims, 2) that the holding in *Fressola* is in the context of omnibus claims, and 3) the inapplicability of the *Fressola* holding. Moreover, Applicants demand that - in view of the unnecessary costs caused by this gross error - the Examiner withdraw finality and permit applicants to get a refund for the expense of yet another RCE!

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[1] If the Examiner is not familiar with what an omnibus claim is, reference can be made to section 2173.05(r) of the MPEP.

[2] One would hope that an examiner who is not credentialed in the law would take extra care to ensure that the legal assertions in an Office Action are correct.

B. All Claim Terms Are Definite

Claims 1, 5-8 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. The Examiner is reminded that well settled law holds that the "definiteness" of claim language must be analyzed, not in a vacuum, but in light of: 1) the content of the particular application's disclosure; 2) the teachings of the prior art; and 3) the claim interpretation apparent to one possessing an ordinary level of skill in the art (at the time the invention was made). See, *In re Marosi*, 218 USPQ 289 (Fed. Cir. 1983); *Rosemount, Inc. v. Beckman Instruments, Inc.*, 221 USPQ 1 (Fed. Cir. 1984) and *W.L. Gore & Associates, Inc. v. Garlock, Inc.* 220 USPQ 303 (Fed. Cir. 1983). Furthermore, this legal standard is promulgated in § 2173.02 of the MPEP. Applicants respectfully submit the Examiner has not applied the accepted analysis, outline above, in favor of the Examiner's personal standard regarding the "definiteness" of the pending claim set. The Examiner's standard cannot sustain a rejection under 35 U.S.C. § 112, second paragraph.

The Examiner argues the rejected claims are "written in functional language and therefore, broader than the enabling disclosure."[3] The Examiner then extracts phrases out of claim 1, and offer the same as evidence of the alleged overbreadth of the pending claims. Specifically, the Examiner suggests that the recitation of such phrases as "conjugating the fluorophore with a biomolecule" and "determinable wavelength" somehow compromise the definiteness of the invention as claimed.

As a threshold objection, the Applicants challenge the Examiner assertion that the invention need be described in the claims. That is to say, the Examiner asserts that the Applicants need "recite the reagents, the reaction times, pH, equipment, and reactions conditions involve[d] in the process."[4] The Examiner's statement is contrary to law. Specifically, "the patent law does not require that all possible [connections] be listed in the patent, let alone that they be listed in the claims." *Orthokinetics Inc. v. Safety Travel Chairs Inc.*, 806 F.2d 1565, 1576 (Fed. Cir. 1986). The relevant inquiry (*vis-a-vis* compliance with 35 U.S.C. § 112, second paragraph) is whether those, skilled in the art, would understand the scope of the claim when the claim is read in light of the specification.

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[3] Office Action Mailed September 17, 2002. Page 2, paragraph 3.

[4] *Id.* at pp. 2-3.

The Applicants have, as precisely as the subject matter permits, reasonably apprised the scope of the claims to those of skill in the art. See, *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367 (Fed. Cir. 1986).

With regard to the phrase "conjugating the fluorophore with a biomolecule," the Applicants provide a detailed description in terms of the definition offered for "fluorophores." Specifically, the specification recites that fluorophores (including but not limited to rhodamine) "have the 3-position carboxylate converted to a fully substituted amide."[5] Furthermore, these fluorophores have "functional groups linked through the 3-position carboxyl group, the linkage converts the 3-position carboxylate to a non-acidic function (e.g., amide), which confers better stability to derivatives such as phosphoramidites."[6] Therefore, "conjugating the fluorophore with a biomolecule" is clearly defined by the aforementioned 3-position carboxyl group chemistry.

With regard to the phrase "determinable wavelength" the specification recites that, "[i]n general, the derivatives and conjugates of this invention are excitable with a light at a wavelength of 500 to 700 nm and fluoresce at a wavelength of 520 to 750 nm."[7] Furthermore, selected rhodamine based dyes of the present invention possess "the fluorescence excitation and emission properties. . .similar to rhodamines used in commercially available automated fluorescent DNA sequencing and fluorescent assay detection instrumentation, with improved spectral separation from commonly used fluorescein derivatives."[8] The Examiner is reminded that words of degree in claims are not indefinite if the specification provides a standard for measuring that degree. See, *Seattle Box Co., Inc. v. Industrial Crating & Packing, Inc.*, 731 F.2d 818 (Fed. Cir. 1984). The specification of the instant application, as described above, provides both specific examples of "determinable wavelength" (e.g. specific excitation / fluorescence wavelengths) and functional examples (e.g. emission properties. . .similar to rhodamines used in commercially available automated fluorescent DNA sequencing

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[5] Specification, pg. 3, lines 18-19.

[6] Specification, pg. 5, lines 20-23.

[7] Specification, pg. 8, lines 8-10.

[8] Specification, pg. 8, lines 3-7.

and fluorescent assay) of "determinable wavelength." These teachings in the specification provide tangible standards for "determinable wavelength" and, thereby, make definite the use of this phrase.

The Examiner sets forth the proposition that "a process claim must recite at least one positive step" and, further, "the positive step must set forth the 'how to' not 'what'."[9] While the Examiner cites the "MPEP" as authority, no specific citation is provided. Applicants respectfully note the MPEP actually states that, "[a] claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced." MPEP § 706.03(d). All of the pending claims in the instant application are compliant with this directive in the MPEP. That is to say, each of the method claims (pending in the instant application) recites numerous "positive steps" in support of "how" an organic compound is labeled for fluorescent detection. These steps include, but are not limited to, i) providing a fluorophore and ii) conjugating the fluorophore with a biomolecule.

C. 35 U.S.C. §112 (Second Paragraph) Does Not Limit The Scope Of The Claims To A Specific Example

The Examiner suggests that, in the event the application is allowed, the Applicants should be limited to the conjugation of only proteins with a fluorophore wherein the resulting conjugate has an excitation wavelength in the range of 500-700 nm and a fluorescent wavelength in the range of 520-750 nm. Once again the Examiner is reminded the fact, "that a claim may be broader than the specific embodiment disclosed in a specification is in itself of no moment." *In re Rasmussen*, 211 USPQ 323, 327 (C.C.P.A. 1981). The metes and bounds of the invention, as claimed, should not be confined to the particulars of a given example. Furthermore, contrary to the Examiner's statement, the Applicants have never suggested that the scope of the present invention should be, "limited to the specific process of making only protein conjugates."[10] While specific examples for the conjugation of proteins are described in the instant application, the specification is comprehensive enough to teach the conjugation of a flurophore with a biomolecule selected from the group consisting of an

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[9] Office Action mailed 09/17/02, page 3, paragraph 2.

[10] Office Action Mailed 09/17/02, page 3, paragraph 3.

amino acid, peptide, protein, nucleotide, oligonucleotide, nucleic acid, cell surface membrane and viral coat.

However, in order to advance their business interests and without acquiescing to the Examiner's argument, while expressly reserving the right to prosecute the claims as originally filed (or claims similar thereto), Applicants have added a new set of claims (e.g. claims 23-25) wherein the conjugated biomolecule is restricted to a protein.

In sum the Applicants maintain the amendments and arguments, offered above, traverse the Examiner's rejections, under 35 U.S.C. § 112 (second paragraph), of claims 1 and 5-8. The Applicants respectfully request, therefore, this rejection be withdrawn.

2. The Claims Are Not Obvious

The Examiner states that "Claims 10-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mayer *et al.*, US 4,647,675, in view of Arnost [Earnest] *et al.*, US 4,900,686, and Kang [King] US 5,846,737."[11]

A. The Examiner Fails To Apply The Requisite Analysis

i. The Examiner Recycles The Same Flawed Rejection

In their papers filed on February 23, 2001 and October 23, 2001, the Applicants set out the standards (under the law) the Examiner must meet in order to establish a *prima facie* case of obviousness. Subsequently, the Applicants provided a detailed analysis documenting how: i) the Examiner failed to provide (any evidence based) motivation to combine the references, ii) even if improperly combined the cited references do not teach each element of the claims, iii) that U.S. patent 4,647,645 is non-analogous art, and iv) the other references cited by the Examiner teach different conjugates. Instead of substantively rebutting the Applicants' arguments (in the pending Office Action), the Examiner has *merely interspersed conclusory captions* into the (almost verbatim) "103" rejections offered in the previous two Office Actions. The Applicants stand on their arguments, set out in their papers captioned above, and believe these same arguments defeat all pending rejections under 35 U.S.C. § 103.

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[11] Office Action Mailed 09/17/02, page 4, paragraph 3.

ii. The Examiner's Remarks Do Not Rehabilitate The Mayer *et al.*, Arnost *et al.* and Kang References

Previously the Applicants rebutted, with specificity, all of the art raised by the Examiner in the rejection under 35 U.S.C. § 103. In addition, the Applicants argued that Mayer *et al.* is **non-analogous art** and that Arnost *et al.* and Kang teach conjugates having **a different chemical synthesis basis** (i.e., lactam ring formation and sulfate conjugates). The Examiner admits that, "a prior art reference must either be in the field of the applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the applicant was concerned, in order to be relied upon as a basis for rejection of the claimed invention."[12] [Citing *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992)].

The only "use" for the compound disclosed by Mayer *et al.* is directed to the dying of fibers and the preparation of printing inks. Specifically, Mayer *et al.* teach,

> "[t]he compounds of the formula I are useful for dyeing anionically modified fibers, for the preparation of printing pastes and printing inks, and for dyeing leather and plastics and in particular paper stocks. Surprisingly, these compounds can also be used for dyeing bleached (wood-free or low-wood) pulps in brilliant red hues."[13]

That is to say, Mayer *et al.* describe (in part) the *cosmetic* dyeing of leather, plastics and paper stocks. In contrast, the Applicants describe the *labeling of biolmolecules with a fluorophore* which (in selected embodiments) are useful as reagents in biochemical diagnostic assays. This excerpt from the cited art demonstrates, therefore, that Mayer *et al.* is not "in the field of the applicant's endeavor" and, thereby, fails the first prong of the "*Oetiker*" test as offered by the Examiner.

As noted in prior papers filed by the Applicants, the law requires the art cited by the Examiner (in order to be considered "analogous") be directed to the essentially the same function and purpose as the claimed invention. See, *In re Deminski* 796 F.2d 436 (Fed. Cir. 1986). If the cited art does not have the same purpose, an inventor would be less motivated to consider it. See, *In re Clay*, 966 F.2d 656 (Fed. Cir. 1992). Applying these legal

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[12] Office Action Mailed 09/17/02, page 6, paragraph 2.

[13] U.S. Patent 4,647,657 to Mayer et al., Col. 3, ll 20-25.

standards, it is clear that compositions "useful for dyeing paper stocks"[14] (as described by Mayer *et al.*) are not relevant or dispositive to the present *methods* for conjugations as claimed in the present invention. That is to say, the teachings provided by Mayer *et al. are clearly not*, pertinent to the particular problem with which the applicant was concerned and, thereby, fail the second prong of the "*Oetiker*" test. Applicants respectfully submit that Mayer *et al.* is properly categorized as *non-analogous art* according to the very standard, offered by the Examiner, to evaluate the same.

Once again, The Examiner is reminded the Applicants are not claiming, in the present application, linking groups as a composition of matter. That is to say, Arnost *et al.*, are silent on the specific *methods* of conjugation claimed in the present invention such that an organic compound *is not conjugated* through the Ra' substituent set out in the invention as claimed.

Also, as noted in Applicants previous correspondence of record, U.S. patent 5,846,737 to Kang *teaches away* from the present invention. That is to say, Kang is directed exclusively to conjugates of *sulforhodamine*. In view of the present invention, the sulphate group on a sulforhodamine causes an unfavorable stearic interaction which substantially prevents the conjugation of an organic compound with a flurophore as claimed. The Examiner is reminded that a reference which teaches away from the invention as claimed is evidence of the *non-obviousness* of this same invention as claimed. That is to say, the Federal Circuit has held the discovery of a method, in the face of prior art which suggests that such a method would produce unacceptable results, is the antithesis of obviousness. See, *In re Hedges*, 228 USPQ 685, 687 (Fed. Cir. 1986).

Despite the deficiencies of the cited art, the Examiner attempts to rehabilitate the same by saying, "the totality of applicant's contention is directed toward anticipatory rejection while the rejection is obviousness type."[15] This is sophistry. The Applicants' have challenged the art cited by the Examiner with arguments that settled law deems appropriate for the rebuttal of a rejection under 35 U.S.C. §103.

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[14] See, Abstract of U.S. Patent 4,647,657 to Mayer *et al.*

[15] Office Action Mailed 09/17/02, page 6, paragraph 2.

Finally, the Examiner admits

> "that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art."[16]

The Applicants have, in previous correspondence, scrupulously documented the Examiner's consistent failure to provide any (evidence based) motivation for the combination of the cited art. That is to say, Applicants have shown how Mayer *et al.* provides no motivation (or suggestion) for the conjugation of rhodamine and, therefore, cannot be properly combined with either Arnost *et al.* or Kang. In addition, Applicants have documented how all of the cited art is silent on the resistance of lactam ring formation during the conjugation of rhodamine at a 3-carboxylamide position (which is recited as a claim element).

Notwithstanding the specific evidence offered by the Applicants regarding, i) the Examiner's failure to make a *prima facie* case of obviousness and ii) the deficiencies (even if improperly combined) of the cited art; the Examiner continues to perpetuate the faulty rejection, under 35 U.S.C. §103, with bald conclusion. Specifically, the Examiner appears to rest his rejection on his allegation that, "it is well known in the art that rhodamine dyes are used in making protein conjugates."[17] This statement is problematic because the Examiner has a burden to present "evidence" with a "clear and particular" showing. Importantly, since an Examiner is NOT one skilled in the art (under the law), the Examiner's opinion on what one skilled in the art might (or might not) believe is of no moment. *In re Rijckaert*, 9 F.3d 1531, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993) ("[T]he examiner's assumptions do not constitute the disclosure of the prior art.").

Of course, if the Examiner has knowledge of relevant facts which are used to make the rejection, the Examiner is free to use those facts - but only if submitted in the form of an affidavit. In the present case, the Examiner has submitted no such affidavit. That is to say, the Examiner has both failed to cite (with particularity) any evidence suggesting the combination of the art which would recapitulate the invention as claimed and has also failed

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[16] Office Action Mailed 09/17/02, page 6, paragraph 3.

[17] Office Action Mailed 09/17/02, page 7, paragraph 1.

to provide an affidavit in support of *his opinion* that "it is well known in the art that rhodamine dyes are used in making protein conjugates." In view of the above, therefore, the Applicants respectfully request the Examiner withdraw the pending rejection under 35 U.S.C. §103.

CONCLUSION

Applicants believe the amendment and arguments, set forth above, traverse the Examiner's rejections and request these grounds for rejection be withdrawn and that the pending claims be passed to allowance. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, Applicants encourage the Examiner to call the undersigned collect at 617.252.3353.

Dated: March 17, 2003

Thomas W. Brown
Registration No. 50,002

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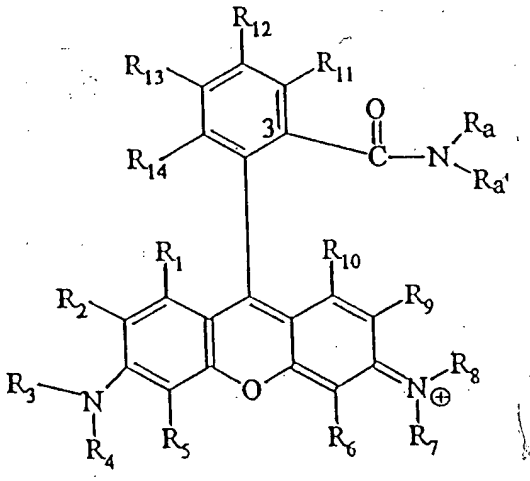
617.252.3353

APPENDIX I
CLEAN SET OF ALL PENDING CLAIMS
PURSUANT TO 37 CFR § 1.121 (c)(3)

1. A method of labeling an organic compound for fluorescent detection, comprising: providing a fluorophore having the structure illustrated by Formula A

FORMULA A



where R_1 and R_{10} taken alone are hydrogen or halogen; R_2, R_5, R_6 and R_9 taken alone are hydrogen, alkyl, carboxyalkyl, aminoalkyl, alkylether, alkylthioether, halogen or alkoxy; R_3, R_4, R_7 and R_8 taken alone are hydrogen, and substituted or unsubstituted alkyl, carboxyalkyl, aminoalkyl, cycloalkyl, aryl; R_2 and R_3 taken together are alkyl chains each having from 2 to 5 carbon atoms connecting the 2′ carbon to the nitrogen attached to the 3′ carbon; R_9 and R_8 taken together are alkyl chains each having from 2 to 5 carbon atoms connecting the 7′ carbon to the nitrogen attached to the 6′ carbon; R_4 and R_5 taken together are alkyl, each having from 2 to 5 carbon atoms connecting the 4′ carbon to the nitrogen attached to the 3′ carbon; R_6 and R_7 taken together are alkyl, each having from 2 to 5 carbon atoms connecting the 5′ carbon to the nitrogen attached to the 6′ carbon; R_3 and R_4 taken together form an alkyl or alkylene chain containing up to 5 atoms in the principal chain, consisting of carbon and one or more heteroatoms from the group consisting of nitrogen or oxygen, with both terminal

valence bonds of said chain being attached to the nitrogen attached to the 3′ carbon; R_7 and R_8 taken together form an alkyl or alkylene chain containing up to 5 atoms in the principal chain, consisting of carbon and one or more heteroatoms from the group consisting of nitrogen or oxygen, with both terminal valence bonds of said chain being attached to the nitrogen attached to the 6′ carbon; R_{11}, R_{12}, R_{13}, and R_{14} are each hydrogen or halogen, where R_a and $R_{a'}$ are selected from the group consisting of alkyl, carboxyalkyl, aminoalkyl, cycloalkyl, aryl and arylalkyl, wherein R_a confers resistance to lactam ring formation, and further wherein $R_{a'}$ contains a functional group; and,

conjugating the fluorophore with a biomolecule selected from the group consisting of an amino acid, peptide, protein, nucleotide, oligonucleotide, nucleic acid, cell surface membrane and viral coat through the $R_{a'}$ functional group of the fluorophore, the resultant conjugate being fluorescent upon excitation with light of a determinable wavelength.

5. The method as in claim 1 wherein the biomolecule is attached to a solid support.

6. The method as in claim 1 wherein the biomolecule is an oligonucleotide and the fluorophore is attached via a phosphoramidite at the 5′ end in the conjugate.

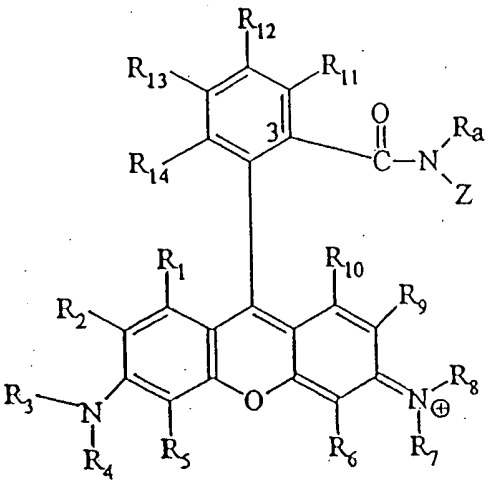
7. The method as in claim 5 wherein the biomolecule is an oligonucleotide and the fluorophore is attached at the 3′ end in the conjugate.

8. The method as in claim 1 wherein the biomolecule is an amino acid, a peptide or a protein, and the fluorophore is attached at an amine or sulfhydryl in the conjugate.

10. A fluorophore conjugate comprising:

a conjugated substance and a fluorophore, the conjugated substance being an amino acid, peptide, protein, nucleotide, oligonucleotide, or nucleic acid to which is attached one or more fluorophores, the fluorophore conjugate having the structure illustrated by Formula 1

FORMULA 1



where R_1 and R_{10} taken alone are hydrogen or halogen; R_2, R_5, R_6 and R_9 taken alone are hydrogen, alkyl, carboxyalkyl, aminoalkyl, alkylether, alkylthioether, halogen or alkoxy; R_3, R_4, R_7 and R_8 taken alone are hydrogen, and substituted or unsubstituted alkyl, carboxyalkyl, aminoalkyl, cycloalkyl, aryl; R_2 and R_3 taken together are alkyl chains each having from 2 to 5 carbon atoms connecting the 2′ carbon to the nitrogen attached to the 3′ carbon; R_9 and R_8 taken together are alkyl chains each having from 2 to 5 carbon atoms connecting the 7′ carbon to the nitrogen attached to the 6′ carbon; R_4 and R_5 taken together are alkyl, each having from 2 to 5 carbon atoms connecting the 4′ carbon to the nitrogen attached to the 3′ carbon; R_6 and R_7 taken together are alkyl, each having from 2 to 5 carbon atoms connecting the 5′ carbon to the nitrogen attached to the 6′ carbon; R_3 and R_4 taken together form an alkyl or alkylene chain containing up to 5 atoms in the principal chain, consisting of carbon and one or more heteroatoms from the group consisting of nitrogen or oxygen, with both terminal valence bonds of said chain being attached to the nitrogen attached to the 3′ carbon; R_7 and R_8 taken together form an alkyl or alkylene chain containing up to 5 atoms in the principal chain, consisting of carbon and one or more heteroatoms from the group consisting of nitrogen or oxygen, with both terminal valence bonds of said chain being attached to the nitrogen attached to the 6′ carbon; R_{11}, R_{12}, R_{13}, and R_{14} are each hydrogen or halogen, where R_a is an alkyl, carboxyalkyl, aminoalkyl, cycloalkyl, aryl, or arylalkyl having from 1 to 10 carbon atoms, and Z represents a linker plus the conjugated substance, wherein said conjugated substance lacks a lactam ring.

11. The conjugate as in claim 10 wherein the conjugated substance is bound to the fluorophore through an amide, ester, ether, disulfide, or thioether linkage.

12. The conjugate as in claim 10 wherein the linkage between the fluorophore and conjugated substance has a phosphate ester.

13. The fluorescent conjugate as in claim 10 wherein the conjugated substance is attached to a solid support.

14. The fluorescent conjugate as in claim 13 wherein the solid support is controlled pore glass.

15. The fluorescent conjugate as in claim 13 wherein the solid support is a polymer support.

16. The fluorescent conjugate as in claim 10 wherein the conjugated substance is part of a cell membrane.

17. The fluorescent conjugate as in claim 10 wherein the conjugated substance is part of a viral coat.

18. The fluorescent conjugate as in claim 10 wherein the fluorophore is derived from tetramethylrhodamine.

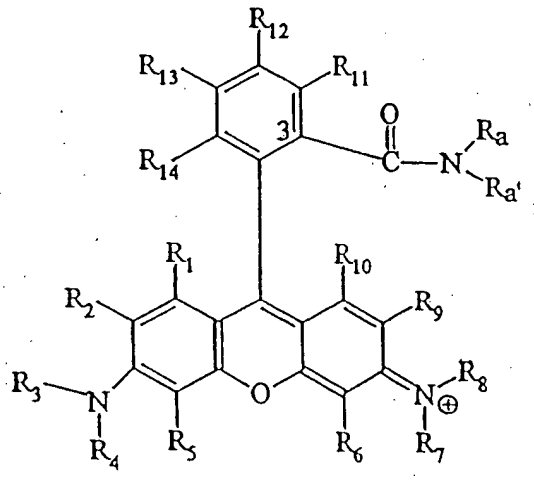
19. The fluorescent conjugate as in claim 10 wherein the fluorophore is derived from rhodamine 101.

20. The fluorescent conjugate as in claim 10 wherein the fluorophore is derived from rhodamine B.

21. A method of labeling a protein for fluorescent detection, comprising:

providing a fluorophore having the structure illustrated by Formula A

FORMULA A



where R_1 and R_{10} taken alone are hydrogen or halogen; R_2, R_5, R_6 and R_9 taken alone are hydrogen, alkyl, carboxyalkyl, aminoalkyl, alkylether, alkylthioether, halogen or alkoxy; R_3, R_4, R_7 and R_8 taken alone are hydrogen, and substituted or unsubstituted alkyl, carboxyalkyl, aminoalkyl, cycloalkyl, aryl; R_2 and R_3 taken together are alkyl chains each having from 2 to 5 carbon atoms connecting the 2′ carbon to the nitrogen attached to the 3′ carbon; R_9 and R_8 taken together are alkyl chains each having from 2 to 5 carbon atoms connecting the 7′ carbon to the nitrogen attached to the 6′ carbon; R_4 and R_5 taken together are alkyl, each having from 2 to 5 carbon atoms connecting the 4′ carbon to the nitrogen attached to the 3′ carbon; R_6 and R_7 taken together are alkyl, each having from 2 to 5 carbon atoms connecting the 5′ carbon to the nitrogen attached to the 6′ carbon; R_3 and R_4 taken together form an alkyl or alkylene chain containing up to 5 atoms in the principal chain, consisting of carbon and one or more heteroatoms from the group consisting of nitrogen or oxygen, with both terminal valence bonds of said chain being attached to the nitrogen attached to the 3′ carbon; R_7 and R_8 taken together form an alkyl or alkylene chain containing up to 5 atoms in the principal chain, consisting of carbon and one or more heteroatoms from the group consisting of nitrogen or oxygen, with both terminal valence bonds of said chain being attached to the nitrogen attached to the 6′ carbon; R_{11}, R_{12}, R_{13}, and R_{14} are each

hydrogen or halogen, where R_a and $R_{a'}$ are selected from the group consisting of alkyl, carboxyalkyl, aminoalkyl, cycloalkyl, aryl and arylalkyl, wherein R_a confers resistance to lactam ring formation, and further wherein $R_{a'}$ contains a functional group; and,

conjugating the fluorophore with a protein through the $R_{a'}$ functional group of the fluorophore, the resultant conjugate being fluorescent upon excitation with light of a determinable wavelength.

22. The method as in claim 21 wherein said protein is attached to a solid support.

23. The method as in claim 21 wherein said protein is attached at an amine or sulfhydryl in said conjugate.